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Pharmacy of the University Medical Center Mainz, Mainz, Germany

S. Kim, I. Krämer

sunhee.kim@unimedizin-mainz.de

Physicochemical stability of Carfilzomib (Kyprolis®) containing solutions after reconstitution and ready-to-administer preparations

Introduction

Kyprolis® powder for solution for infusion containing carfilzomib as active pharmaceutical ingredient is indicated in combination with lenalidomide and dexamethasone to treat multiple myeloma in adult patients who have received at least one previous treatment, including bortezomib for their cancer. Carfilzomib is a second-generation, selective and irreversible proteasome inhibitor.

The purpose of this study was to determine the physicochemical stability of carfilzomib solution. The stability of reconstituted Kyprolis® powder in glass vials and diluted solution stored in plastic syringes and polyolefin (PO) infusion bags should be determined after storage under refrigeration or at room temperature (RT) for 28 days.

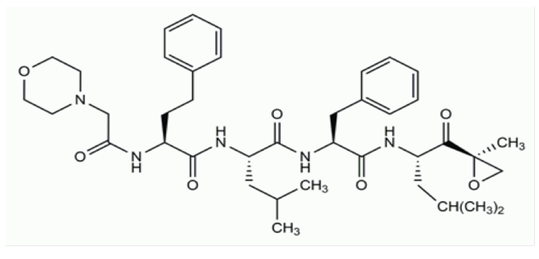

Figure 1: Chemical structure of carfilzomib

Methoden

Chemical stability of Kyprolis® solutions: Validated stability-indicating RP-HPLC assay with PDA detection[1,2].
Physicochemical stability: Measurement of pH-values, visual inspection for color changes and particulate matter.

Reconstituted Kyprolis® solutions (2 mg/mL) and ready-to-administer preparations in plastic syringes (0.8 mg/mL) and PO infusion bags (0.6 mg/mL) were prepared according to the SmPC. The test solutions stored under refrigeration (2-8 °C) or at RT (25 °C) were analysed at predetermined intervals over a maximum storage period of 28 days. Each sample of test solutions was injected by an autosampler in triplicate.

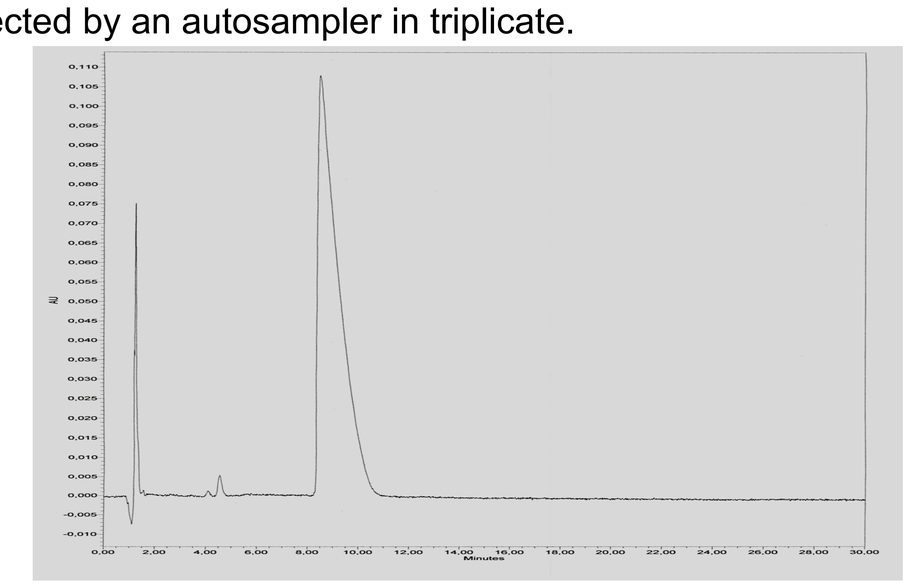

Figure 2: Representative HPLC-chromatogram of freshly prepared carfilzomib solution (Kyprolis®) in dextrose 5% (0.2 mg/mL)

Conclusion

Reconstituted Kyprolis® solutions and diluted infusion solutions in plastic syringes and PO infusion bags are stable for at least 14 days and 10 days, respectively when stored at RT. Refrigerated carfilzomib solutions are stable in glass vials after reconstitution as well as diluted infusion solutions in plastic syringes and PO infusion bags over a period of at least 28 days.

Results

In test solutions stored under refrigeration carfilzomib concentrations were only slightly decreased (100 ± <6%) at the end of the test period independent from the concentration or type of primary container. In reconstituted test solutions stored at RT carfilzomib concentrations fell below 90% of the initial concentration from day 14 of storage onward. In all test solutions the pH-values remained unchanged. No particulate matter or color changes were observed over the test period.

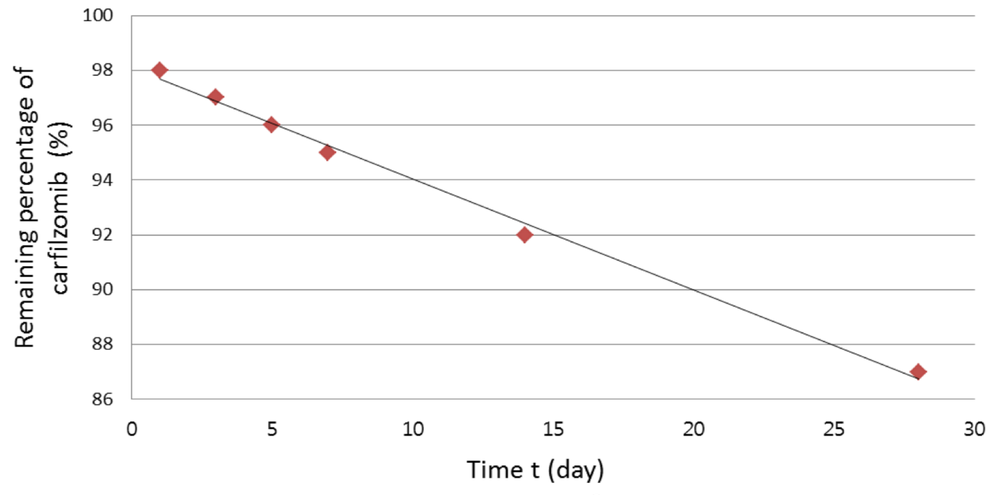

Figure 3: Degradation rate of carfilzomib in Kyprolis® containing solution (2 mg/mL) in plastic syringes stored at RT (25 °C).

Table 1: Stability of reconstituted carfilzomib solutions in glass vials over a period of 28 days, stored under refrigeration (2-8 °C) (n=9)

Carfilzomib concentration [mg/mL]		% Initial concentration remaining ± relative SD					
Nominal	Day 0	Day 1	Day 3	Day 5	Day 7	Day 14	Day 28
2.0	2.02±0.3	101±0.3	99.2±0.2	100.4±0.4	98.1±0.2	99.2±0.2	98±0.5
Drug concentrations in samples taken at time zero were designated as 100%; n=9							

Table 2: Stability of diluted carfilzomib solutions in plastic syringes and PO infusion bags over a period of 28 days, stored under refrigeration (2-8 °C) (n=9)

Container Material	Carfilzomib concentration [mg/mL]	% Initial concentration remaining ± relative SD										
	Nominal	Day 0	Day 0			Day 1 (24h)	Day 2	Day 3	Day 4	Day 5	Day 7	Day 14	Day 28
			3h	6h	12h								
Plastic syringe	0.8	0.78 ±0.4	100.2 ±0.1	100.6 ±0.2	99.9 ±0.2	100.1 ±0.0	100.2 ±0.1	100.4 ±0.0	99.3 ±0.2	99.7 ±0.2	100.3 ±0.2	98.8 ±0.2	96.6 ±0.0
PO infusion bag	0.6	0.60 ±0.1	n. d.			102.1 ±0.2	n. d.	101.5 ±0.3	n. d.	100.6 ±0.2	101.3 ±0.3	100.6 ±0.3	98.6 ±0.4
Drug concentrations in samples taken at time zero were designated as 100%; n=9													

Literature

(1)Hayes ME et al. Remote loading of sparingly water-soluble drugs into liposomes. US Patent Application Publication 2014

(2)Garg A et al. Effect of Captisol and pH on the Stability of Carfilzomib (CFZ) in Drug Product under Oxidative Degradation. Available from: http://abstracts.aaps.org/Verify/AAPS2015/PosterSubmissions/W5165.pdf.